REMARKS/ARGUMENTS

The Examiner indicated that the specification was objected to under 35 USC §132 as incorporating new matter regarding the reference of Raines added in the previous amendment. Applicants herein delete the language referring to the Raines reference at page 5, lines 12-19, and now submit that this rejection is overcome.

At the outset, Applicants acknowledge with appreciation the Examiner's rejoinder of claims 10, 24 and 40, and the withdrawal of rejections outlined in paragraphs 1, 2, and 3 of the outstanding Office Action. Accordingly, following entry of the present amendment, claims 1-3, 5-11, 13-17, 19-25, 27-33, 35-41, 43-45, and 58-78 remain in the application for consideration. Claims 58-78 are newly presented. Claims 4, 12, 18, 26, 34, and 42 were cancelled in the previous Office Action Reply submitted November 21, 2002. Original claims 46-57 were cancelled without prejudice in the Reply submitted by Applicants on April 26, 2002.

Claim Objections

Claims 10 and 24 were objected because they depend from rejected base claims, but were indicated as being allowable if rewritten in independent form.

To address the objections, Applicants herein present new claims 58-78 for consideration. Briefly, claims 58-67 recite a molecular delivery vehicle similar to claim 1, and includes the limitation that the targeting portion of the recombinant targeting fusion protein is vascular endothelial growth factor 121, as recited in claim 10. In addition, claims 68-78 recite a pharmaceutical composition similar to claim 15, and includes the limitation that the targeting portion of the recombinant targeting fusion protein is vascular endothelial growth factor 121, as recited in claim 24.

Applicants submit that new claims 58 and 68, as well as claims depending therefrom, are now allowable.

Applicants also herein correct a typographical error wherein "bids" is recited, but "beads" was intended. These typographical errors occur in the paragraph at page 15, lines 13-19, and claims 6, 20, and 36. Applicants submit that the corrections incorporate no new matter.

Rejections under 35 USC §112

Claims 8, 11, 22, 25, 38, and 41 were rejected under 35 USC §112, first paragraph, as allegedly containing new subject matter by the addition of "ribonuclease I" and the Raines reference in the previous Office Action reply. Claims 8, 11, 22, 25, 38, and

41 were also rejected under 35 USC §112, second paragraph, as allegedly failing to particularly point out and distinctly claim the invention. Applicants respectfully traverse these rejections.

With regard to the rejection under 35 USC §112, first paragraph, the Examiner indicated Applicants have not provided a copy of the Raines reference to show homology between ribonuclease A and ribonuclease I. Applicants enclose herewith a copy of Raines, "Ribonuclease A", *Chem. Rev.* **98**:1045-1065 (1998) for the Examiner's convenience, showing that bovine ribonuclease A and ribonuclease I from human pancreas are homologous. In particular, at page 1045, the article refers to "bovine ribonuclease A", in which the "A" refers to the predominant form of the enzyme in the pancreas of *Bos taurus* (a cow or bovine).

Moreover, on page 1059 of the Raines article, the last paragraph states "Humans contain at least five homologues of RNase A (Figure 10)" and goes on to mention RNase I. Further, the legend to Figure 10 states "Amino acid sequences of RNase A ... and five human homologues (RNase 1, RNase 2, RNase 3, RNase 4, and angiogenin).". Applicants submit that this reference clearly shows that bovine ribonuclease A and ribonuclease I from humans are homologous.

Additionally, Applicants submit a copy of an MSDS sheet for ribonuclease A from Sigma Chemical Company. As shown on the MSDS sheet, synonyms for ribonuclease A include, among other things, ribonuclease I.

In view of these publications, Applicants submit that the addition of "ribonuclease I" to the specification does not constitute new matter. Rather, since the original language of the specification recited "bovine or human ribonuclease A", and in view of the above citations that show that bovine ribonuclease A and human ribonuclease I are homologous, Applicants submit that the proposed addition clarifies that the human homolog of bovine ribonuclease A is known as ribonuclease I. Thus, Applicants herein amend claims 8, 11, 22, 25, 38, and 41 to recite "human ribonuclease I", and submit that no new matter is added. Applicants therefore submit that this rejection is overcome.

With regard to the rejection under 35 USC §112, second paragraph, Applicants submit that the phrase "ribonuclease I", by itself, is understood by those of skill in the art. As illustrated in the Raines reference cited herewith, RNase I is well known to be an RNase A homolog from human pancreas. Accordingly, Applicants submit that "bovine ribonuclease A or

ribonuclease I" is understood by those of skill in the art, and that this rejection is overcome.

Claims 31-33, 35-41, and 43-45 were rejected under 35 USC §112, first paragraph, for allegedly lacking of enablement. Specifically, it was indicated that while the claims are enabling for methods for delivery of nucleic acid diagnostic compounds and nucleic acid research compounds, enablement is not provided for delivery of therapeutic nucleic acids to a target in a patient.

To address the rejection, Applicants herein delete "therapeutic, diagnostic, or research" from claims 31 and 37, as well as claims 1, 7, 15, 21, and 30, and now submit that this rejection is moot.

Rejections under 35 USC §103

Claims 1-3, 5-9, 13-17, 19-23, 27-29, 31-33, 35-39, and 43-45 were rejected as being unpatentable over U.S. Patent No. 4,885,172 to Bally et al., in view of WO 95/26412 to Curiel. Applicants respectfully traverse the rejection.

Bally et al. disclose a composition for targeting, storing and loading of liposomes consisting of liposomes covalently or non-covalently coupled to the glycoprotein streptavidin. The streptavidin is coupled to biotinylated proteins made by

chemical modifications. Examples of such chemically modified proteins include biotinylated immunoglobulin G or biotinylated monoclonal antibodies. In the rejection, it was asserted that the liposome acts as the carrier, the adapter is streptavidin, and the targeting protein is an antibody, having a recognition portion (e.g., the biotin) and a targeting portion (e.g., the rest of the antibody).

Curiel et al. discloses a fiber protein of adenovirus that has been genetically altered via attachment at the carboxyl end of a peptide linker which can be used to attach a non-adenovirus ligand that alters the binding specification of the fiber protein. Examples of ligands disclosed by Curiel et al. include peptides which are selectively bound by a targeted cell so that the modified fiber protein is internalized, and peptides which can act as a universal coupling agent, such as biotin or streptavidin. The modified fiber protein is prepared by genetic engineering of the nucleotide sequence encoding the fiber protein, through the addition of new sequence at the carboxyl tail-encoding region which encodes the linker and ligand.

Applicants submit that the presently claimed invention is not obvious in view of Bally and/or Curiel. In the previous reply, claims 1, 15, 30, and 31, and claims depending therefrom,

were amended to recite a recombinant targeting fusion protein that is made from a recognition portion, that consists essentially of a recognition peptide, and a targeting portion that is capable of binding to the target. Specifically, claims 1, 15, 30 and 31 were amended to recite a molecular delivery vehicle, comprising:

(a) a carrier for carrying compounds;
(b) an adapter covalently linked to the carrier; and
(c) a recombinant targeting fusion protein comprising a recognition portion and a targeting portion, the recognition portion consisting essentially of a recognition peptide, and capable of binding to the adapter, the targeting portion capable of binding to a target.

In particular, element (c), the recombinant targeting fusion protein, is a unique element in the present invention. As recited above, the recombinant targeting fusion protein comprises a recognition portion and a targeting portion, where the recognition portion consists essentially of a recognition peptide.

Bally et al. does not disclose or suggest a recombinant targeting fusion protein as disclosed and claimed by Applicants, but rather a chemically modified protein. Applicants submit

that the phrase "fusion protein" is defined in the specification at page 13, lines 4-7, wherein it is stated:

> a fusion protein refers to a recombinant protein that contains two or more polypeptide fragments that are encoded by DNA sequences that have been combined with the methods of recombinant DNA technology in a form that allows expression of the fusion protein in suitable hosts. (Emphasis supplied)

The element disclosed by Bally that is most similar to the targeting fusion protein is not a fusion protein at all. Rather, it is a combination of biotin (attached to an antibody) that is noncovalently bound to streptavidin (attached to a liposome). Further, the claims also recite that the recognition portion of the targeting fusion protein consists essentially of a recognition peptide to distinguish it from the reference of Bally et al. which discloses a chemical moiety as a "recognition portion". Thus it is clear that the recombinant fusion protein recited in the claims of the present invention is distinguishable from the chemically modified (e.g., biotinylated) antibodies noncovalently bound to streptavidin-modified liposomes disclosed by Bally et al.

Further, Curiel et al. does not cure the deficiencies of Bally et al. Like Bally et al., Curiel et al. does not disclose or suggest a recombinant targeting fusion protein comprising a recognition portion and a targeting portion, where the

recognition portion consists essentially of a recognition peptide. Rather, Curiel et al. discloses genetic modification of adenovirus fiber protein to include a peptide linker. There is no disclosure or suggestion by Curiel et al. to implement a targeting fusion protein that comprises a recognition portion and a targeting portion, where the recognition portion consists essentially of a recognition peptide.

Accordingly, Applicants submit that the presently claimed invention is not obvious over the combination of Bally et al. and Curiel et al., and that this rejection is overcome.

In view of the above amendments and remarks, Applicants submit that the claims are in condition for allowance, and respectfully request reconsideration and early receipt of a Notice of Allowance.

If a telephone conference would aid in the continued prosecution of this application, the Examiner is invited and encouraged to contact Applicants' representative at the telephone number listed below.

Respectfully submitted,

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Date: 08 AUG 2003

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